Dr Susan M Pilch
Documents Management Branch
HFA 305
U.S.F.D.A
5630 Fishers Lane R1061
Rockville Md 20852

R.F. James
8 Rata St 99 JUN -2 A11:23
WHANGAREI N.Z.
5/22/99

Dear Dr Pilch

Docket 98P-0683
P.T.I: Health Labelling Claims

I enclose this document, which has only just become available, for your file:

Infantile Leukemia and Soybeans - a Hypothesis
Dr T. Abe of the Dept of Hygiene, Kyoto University School of Medicine.
from Leukemia 1999 Mar 13: 3 317 Abstract

Note that the biochemistry is correct. The only reason it can't be demonstrated is because it addresses foetal damage to pregnant women from soy foods

Sincerely
Richard F James

98P-0683

C132

Evaluated MEDLINE

Leukemia • Volume 13 • Issue 3

Infantile leukemia and soybeans--a hypothesis [editorial]

Abe T

Leukemia 1999 Mar 13:3 317-20

Abstract

Recent molecular-genetic studies have revealed that in the majority of patients with secondary leukemia induced by topoisomerase II (topo II) inhibitors and also with infantile acute leukemia (IAL), the breakpoints are clustered within scaffold attachment regions (SARs) of 3'-MLL-bcr near exon 9. Genistein, abundant in soybeans, is reported to be a potent nonintercalative topo II inhibitor. It interferes with the break-reseal reaction of topo II by stabilizing a cleavable complex, which in the presence of detergents, results in DNA strand breaks. The present study revealed that genistein induced chromatid-type aberrations, in which chromatid exchanges are often observed. Genistein seems to act in a manner very similar to that of VP-16, although the latter is reported to produce both chromatid- and chromosome-type aberrations. In view of this pharmacological similarity between genistein and VP-16, and also the similarity of breakpoint clustering regions within the MLL gene in reported cases with secondary leukemia and IAL, genistein may be largely responsible for the development of IAL.

MeSH

Acute Disease, Age of Onset, Carcinogens, Chromosome Banding, Genistein, Human, Infant, Karyotyping, Leukemia, Soybeans, Support, Non-U.S. Gov't

EDITORIAL

Infantile leukemia and soybeans – a hypothesis

T Abe

Department of Hygiene, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan

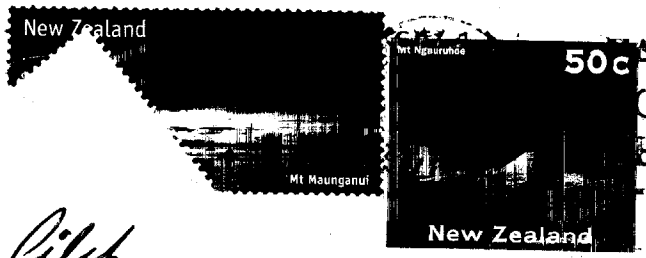
Recent molecular-genetic studies have revealed that in the majority of patients with secondary leukemia induced by topoisomerase II (topo II) inhibitors and also with infantile acute leukemia (IAL), the breakpoints are clustered within scaffold attachment regions (SARs) of 3'-MLL-bcr near exon 9. Genistein, abundant in soybeans, is reported to be a potent nonintercalative topo II inhibitor. It interferes with the break-reseal reaction of topo II by stabilizing a cleavable complex, which in the presence of detergents, results in DNA strand breaks. The present study revealed that genistein induced chromatid-type aberrations, in which chromatid exchanges are often observed. Genistein seems to act in a manner very similar to that of VP-16, although the latter is reported to produce both chromatid- and chromosome-type aberrations. In view of this pharmacological similarity between genistein and VP-16, and also the similarity of breakpoint clustering regions within the MLL gene in reported cases with secondary leukemia and IAL, genistein may be largely responsible for the development of IAL.

Keywords: infantile leukemia; genistein; topoisomerase II inhibitors; scaffold attachment regions (SARs); chromatid exchanges

Infantile acute leukemia (IAL) which usually occurs within the first 12 months of life is characterized by a high leukocyte count at diagnosis, often exceeding 100×10^9/l, the presence of a variety of reciprocal translocations with 11q23 and extremely poor prognosis, regardless of whether the IAL is myeloblastic, monoblastic or lymphoblastic.[1] It seems reasonable to assume that leukemic clones of IAL develop *in utero*. With evidence obtained by long-range PCR using primers spanning the *MLL-AF4* genomic junction applied to Guthrie cards, Cale *et al*[2] have shown that leukemic cells were present at birth in three patients who were diagnosed at 5, 6 and 24 months of age, and presented unequivocal evidence of the that may act to prevent the development of cancer. The former include bracken, royal fern, butterbur flower stalk, pyrolysates, and chemicals made by modern industries, and an example of the latter latter is flavonoids. According to their findings, flavonoids are potentially mutagenic, but they may suppress the progression in carcinogenesis.

Recent studies have shed further light on flavonoids, by identifying a certain degree of chemoprevention by flavonoids of certain classes of cancer. It was found that rapidly proliferating cancer cells at a very early stage could theoretically be killed in the presence of topo II inhibitors, and that thus their growth might be effectively suppressed. On the other hand, it has been suggested that isoflavone phytoestrogens represent a potential hazard for infants, especially for their reproductive organs, as their steric structure closely resembles that of estrogens and they bind weakly to steroidal receptors.[7,8] Daidzein and genistein, aglycones of isoflavones, are found abundantly in soybeans, and their placental transfer has been demonstrated in cord blood analysis.[7] For these reasons, and also because the concentrations of phytoestrogens in soy-based infant formulas are estimated to be several hundred times higher than those in breast milk, these formulas are now the subject of extensive study for elucidation of their potential adverse effects on humans.[8]

Specifically, genistein, known as an undesirable and bitter component of soybeans, is reported to inhibit the activity of tyrosine kinase, p56/p53^{lyn}, but also to rank as a potent topo II inhibitor among the many flavonoid compounds.[9] It interferes with the break-reseal reaction of topo II by stabilizing a cleavable complex, which in the presence of detergents, results in DNA strand breaks. *Unlike adriamycin, actinomycin D, or amsacrine*, genistein is classified as a nonintercalative



Dr Susan Pilch
Documents Management Branch HFA 305
U.S Food & Drug Administration
5630 Fishers Lane # 1061
Rockville Md 20852
U.S.A

20857/0003